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Efficacy of Patient Education and Duloxetine, Alone and in Combination, for Patients With Multisystem Functional Somatic Disorder: Study Protocol for the EDULOX Trial

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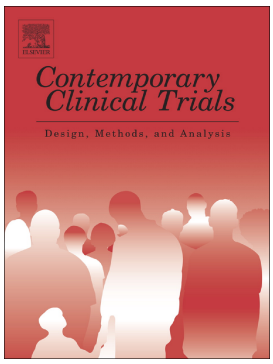

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Efficacy of patient education and duloxetine, alone and in combination, for patients with multisystem functional somatic disorder: Study protocol for the EDULOX trial

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Abbreviations: BDS, Bodily Distress Disorder; EUC, Enhanced Usual Care; FSD, Functional Somatic Disorder; FSS, Functional Somatic Syndromes; PE, Patient Education; RCF, the Research Clinic for Functional Disorders and Psychosomatics; SNRI, serotonin–norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants.

Trial registration number: The study is registered at www.clinicaltrials.gov (NCT06232473) and the internal list of research projects at the Region of Central Denmark (Case number 1-16-02-305-23). Approval from the Danish Medical Research Ethics Committees (Case number: 2212291) and the Danish Medicines Agency was obtained under EudraCT Number: 2022-002780-30 and Sponsor's Protocol Code Number: 9515.

Abstract

Background

Multisystem functional somatic disorder is characterized by specific patterns of persistent physical symptoms with a complex biopsychosocial etiology. The disorder can lead to disability and personal suffering. Current treatment options require specialized settings, therefore patients often wait a long time to receive specific treatment.

Patient education is considered important in most treatment programs, but has only been investigated sparsely as a stand-alone treatment. Pharmacological treatment is limited to tricyclic antidepressants in low doses with no antidepressant properties. Duloxetine has been found effective in single organ functional disorders. As a treatment for multisystem functional somatic disorder, duloxetine could reduce symptoms and treat comorbid anxiety and depression. It may furthermore enhance the effect of patient education through a hypothesized effect on cognitive functioning. The purpose of the EDULOX trial is to study psycho-EDUcation and duLOXetine alone and in combination.

Methods

This is a nested study design. The parent trial "EDULOX1" (n=424) will compare a patient education program with enhanced usual care in an open-labelled, randomised controlled trial. In addition to this, eligible participants will furthermore receive either duloxetine or active placebo in the nested, double-blinded, randomized controlled trial, "EDULOX2" (n=212). Patient and clinician reported outcomes will be collected through questionnaires.

Conclusion

The EDULOX trial may establish evidence for treatments applicable for the majority of patients with multisystem functional somatic disorder. If effective, duloxetine would be a more tolerable pharmacological treatment option that can target comorbid depression and anxiety, and potentially boost the effect of patient education.

1. Background

Functional somatic disorders (FSD) are characterized by specific patterns of persistent physical symptoms with a complex etiology involving a multiform interplay between physiological, psychological, and sociocultural factors [1, 2]. Patients with FSD are prevalent in all medical settings and may receive diagnoses such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and other functional somatic syndromes (FSS) depending on which medical specialty they consult [3, 4]. A severely affected subgroup of patients suffer from multisystem FSD with symptoms from multiple organ systems [5]. The diagnosis is made according to the criteria for the unifying research diagnosis bodily distress syndrome (BDS) [6].

Multisystem FSD affects 1.3-2.2% of the general population [7, 8]. The condition inflicts suffering and is associated with a substantial socioeconomic impact, involving costly - often futile - diagnostic examinations and procedures, sick leaves, and long-term disability [9-11].

Evidence on treatment options for multisystem FSD is emerging but not yet sufficient [1]. A number of clinical trials investigating non-pharmacological interventions are available [12-17], and clinical guidelines for some FSS (e.g., fibromyalgia and chronic primary pain) [18, 19] highlight the importance of patient education (PE) [20, 21]. PE may support the effect of other treatments by empowering and engaging patients in managing their condition [22-24]. As a stand-alone treatment, the effect of PE has only been sparsely investigated, however; a PE program targeting multisystem FSD has been tested in an uncontrolled pilot study with promising results [25].

In clinical practice, centrally acting medications are frequently prescribed to patients with FSS[26], with serotonin–norepinephrine reuptake inhibitors (SNRIs), being the most frequently prescribed class[27] The mechanisms of antidepressant effectiveness in FSS are incompletely understood, but multiple actions are possible. Treating co-morbid depression may impact illness perception, treatment adherence, and behavioural responses to illness [28]. Additionally, there is

evidence for central analgesic effects [29], as well as for reductions in affective arousal and sleep dysfunction [30]. Improved cognitive functioning may be a mediating factor [31-33]. However evidence for pharmacotherapy in FSS is limited [34]. In multisystem FSD, the strongest evidence exists for treatment with low-dose tricyclic antidepressants (TCAs) [35]. Unfortunately, TCAs given in higher doses significantly reduce tolerability and thus also the treatment potential for comorbid depression or anxiety[8]. In clinical practice, SNRIs such as Duloxetine offer a more favorable adverse event profile [32, 33, 36]. Within chronic pain conditions including fibromyalgia, where there is the greatest accumulation of evidence, Duloxetine is ranked superior to other antidepressants, with small to moderate effects on pain scores and small but reliable effects on other outcomes [37].

From a clinical perspective, a synergistic effect between a PE program and pharmacological treatment could be beneficial. On one hand, PE may improve the effect of pharmacological treatment by balancing treatment expectations, thus enhancing treatment adherence. Conversely, pharmacological treatment may indirectly enhance the effect of PE by improving cognitive functioning, thereby improving the patients' ability to benefit from education.

At present, current treatment options for multisystem FSDs are limited as most evidence-based options require highly specialized settings. In order to inform treatment programs suitable for a larger patient population, more knowledge is needed on both psychoeducational and pharmacological options and the combination of these treatments.

2. Aims and hypotheses

The EDULOX trial aims to investigate:

1. the effect of a PE program compared with enhanced usual care (EUC) for patients with multisystem FSD

2. the effect of treatment with duloxetine 60 mg daily against active placebo, and

3. to explore the effect of combinations of the two interventions

To our knowledge this is the first study to investigate the combination of medical treatment and PE in patients with multisystem FSD.

2.1. Hypothesis EDULOX1:

The primary hypothesis is that the PE program is superior to EUC in improving patient-rated health-related quality of life measured by a Short-Form Health Survey (SF-36) aggregate score and patient-rated overall health measured by the Clinical Global Impression - Improvement Scale (CGI-I). Secondary outcomes will be reported, including clinician rated CGI-I.

2.2. Hypothesis EDULOX2:

The primary hypothesis is that duloxetine is superior to active placebo in improving the SF-36 aggregate score, patient-rated CGI-I. Secondary outcomes will be reported, including clinician rated CGI-I.

2.3. Exploratory hypothesis:

There is a synergistic effect of receiving both PE and duloxetine, i.e., participants receiving both interventions show larger improvement in SF-36 aggregate score and patient-rated CGI-I than would be expected from a simple additive effect of each intervention. c

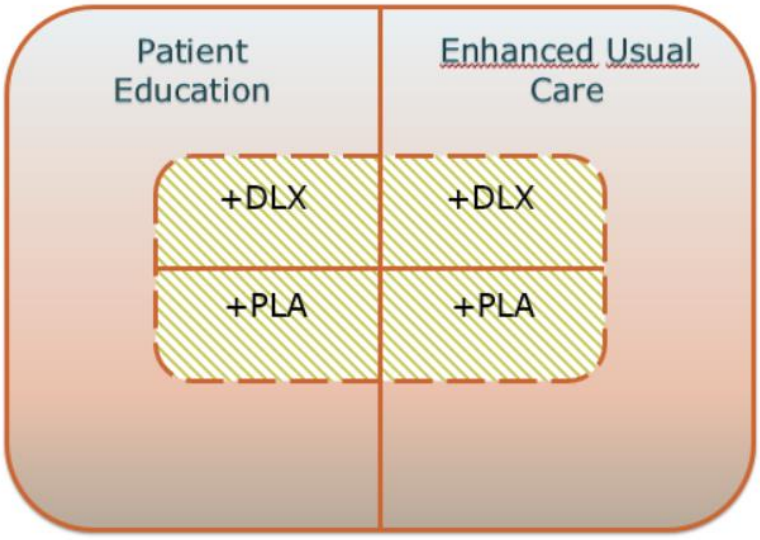
3. Methods

3.1. Study design

In order to test the individual effect of both PE and duloxetine treatment, respectively, and the possible synergistic combination of both interventions, the EDULOX trial uses a nested design (Fig. 1).

Figure 1

Nested study design illustrating the six randomization groups: Patient Education, Patient Education and Duloxetine (DLX), Patient Education and Placebo (PLA), Enhanced Usual Care, Enhanced Usual Care and Duloxetine (DLX), Enhanced Usual Care and Placebo (PLA).



The parent trial (EDULOX 1) is a prospective, open-labelled, randomized controlled trial comparing a PE program with EUC. The parent trial nests a study drug trial (EDULOX2), which is a two-by-two factorial, double-blinded, randomized controlled trial comparing duloxetine with active placebo in combination with the PE program or EUC.

The primary endpoint is week 10, end-of treatment (week 12 after protocol initiation).

3.2. Setting

The project is initiated and managed by the Research Clinic for Functional Disorders and Psychosomatics (RCF), Aarhus University Hospital (AUH), Region of Central Jutland, Denmark. Collaborations with the Pain and Headache Clinic, AUH; the Center for Functional Disorders, Hospital Lillebaelt (Region of Southern Denmark); and the Center for Functional Disorders, Aalborg University Hospital (Region of Northern Jutland) are being developed with the aim of recruiting from a larger geographical area.

3.3. Recruitment and participants

Participants will be recruited from patients undergoing assessment for FSD at the RCF, AUH. At the assessment, the multisystem FSD diagnosis is established by a medical doctor using the diagnostic criteria for multiorgan BDS. To fulfill these criteria, the patient must experience three or more symptoms from three or more symptom clusters (cardiopulmonary including autonomic, gastrointestinal, musculoskeletal and general symptoms). The symptoms must be distressing or result in substantial disability in order to qualify for diagnosis. Furthermore, differential diagnoses must have been considered and investigated when relevant. The assessment includes a diagnostic interview [38]), a physical examination, blood tests, ECG, and a thorough review of medical records [35]. Patients diagnosed with multisystem FSD will be invited to a screening interview 1-2 weeks after the assessment. At the screening interview, participants will be assessed for eligibility for EDULOX1 and EDULOX2. Those eligible for EDULOX2 (PE or EUC in combination with duloxetine or placebo) will be offered participation in EDULOX2. Participants who meet inclusion criteria for EDULOX1 but not the more stringent criteria of EDULOX2, and participants who decline inclusion in EDULOX2, will be offered to take part in the EDULOX1 protocol. Inclusion and exclusion criteria for both protocols are presented in Table 1. This study design optimizes

recruitment as the vast majority of patients will be eligible for EDULOX1, thereby allowing participation even when participants are not eligible to participate in the study drug trial.

Based on the power analysis presented below, a total of 424 participants for the parent trial (EDULOX1) and 212 participants for the nested trial (EDULOX2) will be recruited.

Table 1

Inclusion and exclusion criteria for EDULOX 1 and EDULOX 2

Inclusion criteria - EDULOX 1	***Additional inclusion criteria - EDULOX 2***
A diagnosis of multisystem FSD	Use of efficient contraception for women in the fertile age (contractive pills, intrauterine device, deposit injections of gestagen, subdermal implant, hormone vaginal ring, or transdermal deposit plaster)
Multisystem FSD is the predominant health complaint, i.e., concurrent physical or psychiatric illness is stable and symptoms can be separated from FSD symptoms	Men with a pregnant or non-pregnant female partner in the fertile age must use a condom at sexual activity for the duration of the trial and at least one week after end of study drug treatment
Age 18-60 years	
Understands and speaks Danish fluently and is able to follow and benefit from an educational program	
First-time referral to a specialized clinic for FSD	

Exclusion criteria ***- EDULOX1***	***Additional exclusion criteria*** ***- EDULOX2***
Alcohol, substance or medicine abuse and/or addiction	Current pregnancy or lactation
Current or previous diagnosis of mania, bipolar disorder, psychosis, severe agitation, imminent deliria or psychotic symptoms	Current affective disorder requiring fast initiation or continuation of psychiatric pharmacological treatment or psychiatric monitoring
Participation in psychotherapy or educational programs specifically for FSD within the past 12 months	Concomitant use of CNS-acting drugs (drugs with pain-modulating or antidepressant properties and others) besides paracetamol and ibuprofen (escape medication in restricted doses). When clinically relevant and safe, the prohibited medication is gradually titrated down at the time of study inclusion, prior to randomization, so treatments are discontinued at least 2 weeks before the treatment phase.
Untreated or unstable moderate to severe depression, anxiety or other psychiatric disorders	Concomitant use of drugs interacting with or contraindicating duloxetine treatment (e.g. antidepressants, antidiuretics, antihypertensives, and triptanes)
	Treatment with duloxetine for a period of at least 8 successive weeks within the past 6 months
	Serious or unstable somatic illness (Appendix 1)
	Severe renal impairment with creatinine clearance <30 ml/min. (risk of increased plasma concentration of duloxetine)

	Liver disease with reduced function with affected blood tests (risk of increased plasma concentration of duloxetine)
	Sweat gland disorder (risk of hyperthermia in high temperatures related to use of benztropine)
	Allergy to study medication or excipients in study medication

3.4. Randomization, allocation concealment, and masking

Participants in the parent trial (EDULOX1) will be randomized (open-label) to receive either the PE program or EUC. Participants in the nested trial (EDULOX2) will be randomized to receive either PE or EUC (open-label) along with either duloxetine or active placebo (double-blinded).

Randomization will be carried out using REDCap. Block randomization will be used with varying block sizes of 2, 4, and 6. Coded packs of study drug and active placebo will be produced by the hospital pharmacy according to the randomization schedule. Both duloxetine and placebo will be re-encapsulated by the hospital pharmacy to ensure identical appearance. Participants, clinicians, investigators, and all other staff involved in the conduct or data analysis of the nested trial (EDULOX2) will be masked to study drug treatment allocation for the duration of the study and throughout the data analysis. At the end of treatment, participants and clinicians will be asked to guess the allocated treatment (duloxetine or active placebo) and give the reason behind their guess to evaluate blinding efficacy, which will be reported. Active placebo was chosen with the primary purpose of adequate blinding, as in a previous comparable study, the side effect profile of the active treatment 'unmasked' the allocation relative to inert placebo[35].

3.5. Patient involvement

Including the voice of patient stakeholders has been important for the development of the EDULOX intervention and the main idea of the trial. Patient-rated outcomes have been chosen as primary outcomes in recognition of the patients' experiences of improvement as the actual goal of the treatment. The research is performed in a clinical setting with close ties between clinical and scientific practice to live up to the aim of providing every patient with the opportunity to participate in research as stated in the WHO statement on user empowerment [39]. The content and form of the PE group session have been evaluated by patients through interviews and adjusted accordingly (n=9). Patient interviews have been conducted to evaluate and adjust written educational material (n=5) and graphical presentations (n=8), and adjustments have been made based on patients' perspectives.

4. Interventions

4.1. Patient education program, PE

The PE program consists of three individual sessions and one group session. The first individual session precedes the group session and aims at providing participants with a biopsychosocial and evidence-based understanding of multisystem FSD.

The content and treatment manual of the 3-hour group-based PE session builds on a previous intervention [25] that has been updated with new models of symptom generation and perpetuation [1] and new written and visual materials were developed to support the process of the intervention. 5 patients were interviewed twice during the development process to evaluate the materials. Patient evaluations resulted in adjustment of the length and type of explanations, the illustrations used, and how the material could be integrated and support the patient during the intervention. The group session offers participants the opportunity to meet with peers, and the individual sessions offer the possibility to elaborate and individualize the elements presented in order to enhance the participants'

treatment engagement and self-management. The three individual consultations are performed by the participants' treatment responsible doctor. Illness understanding and illness behaviors are addressed by collaboratively developing an individualized case formulation of the participants' risk factors, precipitating factors, and current perpetuating factors. The treatment manual is presented in Appendix 2.

The quality of the PE intervention will be ensured by providing the project doctors with relevant education (e.g., participation in workshops on the manualized content in the PE program), and through biweekly formal supervision. Clinicians will be able to seek advice regarding the individual sessions on a weekly basis. Adherence to protocol will be monitored by audio recordings of all PE sessions from which a random sample will be analyzed using predefined evaluation points. Compliance and attendance are assessed by registration of all contacts during the trial.

4.2. Enhanced usual care, EUC

After assessment, participants in the EUC group will have three contacts at the clinic: one screening interview, a visit at end of treatment, and a visit 3 months after end-of-treatment to discuss further treatment.

4.3. Duloxetine

Duloxetine is administered in daily doses of 30-60 mg. The most common adverse effects are nausea, headache, dry mouth, and somnolence (Appendix 3). The majority of the adverse events are mild to moderate, start early in therapy, and subside during a few weeks of therapy. A low dose of duloxetine has been chosen in order to enhance tolerability.

4.4. Active placebo

Benztropine is an anticholinergic agent used predominantly in the symptomatic therapy of Parkinson disease and movement disorders and has no positive effect on symptoms of multisystem FSD. When administered in daily doses of 0.5 mg, the adverse events are mainly extensions of its anticholinergic and antihistaminic effects that mimic the side effects of duloxetine. The most commonly reported are nausea and dry mouth [40]. Benztropine will not be used in conditions in which anticholinergic effects are undesirable (e.g., prostatic hypertrophy). Benztropine has been used in previous studies as an active placebo for both TCAs and SSRIs in pain studies [41-43].

4.5. Study drug treatment program

Study drug treatment is initiated at a set point approximately 2 weeks after randomisation. Participants will be guided through the treatment by visits at the clinic (weeks 0, 6, and 10) and phone contact (week 1) performed by a project nurse with access to supervision from project doctors. Information on adverse events and use of other drugs is collected at these contacts. The initial dosage is 30 mg duloxetine/0.50 mg benztropine (one capsule) daily for 2 weeks, after which dosage is increased to 60 mg duloxetine/0.5 mg benztropine (two capsules) daily for 8 weeks. If participants are unable to increase in dose due to adverse events, but tolerate the initial dose, this dose is maintained for the remaining part of the trial. Total duration of the study protocol from randomization to end of treatment is 12 weeks (2 weeks before treatment initiation to allow for preparation of study drugs, 2 weeks of low dose, 8 weeks of full dose). The dose is then reduced to 30 mg duloxetine/0.5 mg benztropine for 1 week and then discontinued. Compliance is evaluated by return of unused capsules, participant-report (open ended questions at clinical visits) and serum duloxetine at the final visit.

5. Data sources and effect measures

5.1. Data collection

Data sources include patient-rated and clinician-rated outcomes, a qualitative evaluation consisting of 10-15 patient interviews examining acceptability, and patient experiences regarding the PE intervention.

Questionnaire data will be collected from all participants at 5 time points:

- T0: Baseline (before inclusion)
- T1: Before randomization
- T2: During treatment
- T3: End of treatment, primary endpoint
- T4: 3-month follow-up after end of treatment

Follow-up measurements are collected at 12 and 24 months from randomization (T5 and T6). Please see Fig. 2 for a detailed flow diagram of the study.

Data at T0 will be obtained from the clinical database FunkData [44] after informed consent. Both patient-rated and clinician-rated outcomes are collected using REDCap, see Table 2 for an overview of outcome measures.

A qualitative evaluation with 10-15 interviews is planned to explore the participants' experiences with the content and acceptability of the PE intervention. These interviews will be conducted during the first year of the trial.

Figure 2

Flow diagram

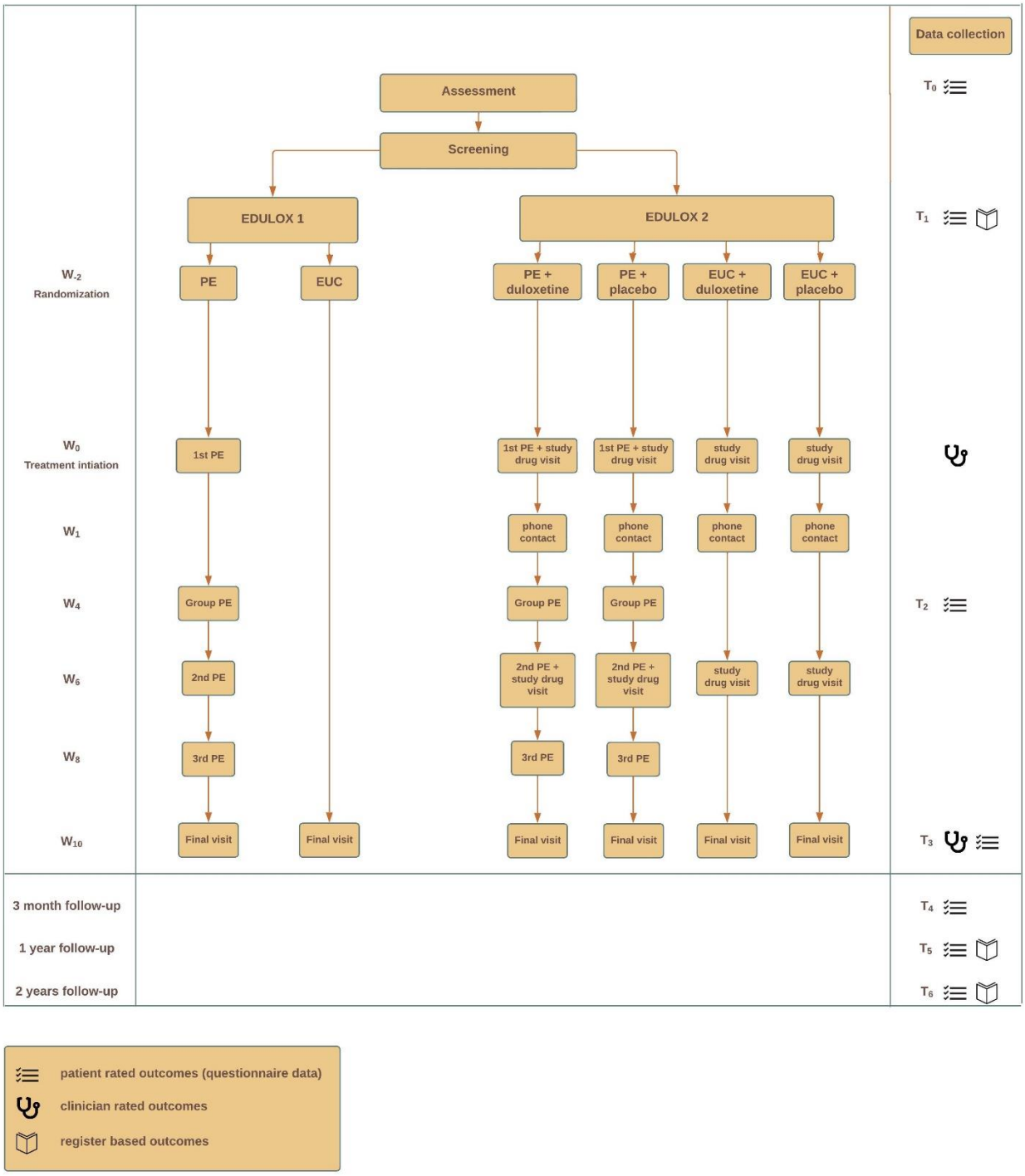


Table 2

Measures and data collection times

*primary outcomes

** only in EDULOX2

Measures	Instrument	T0	T1	T2	T3	T4	T5	T6
Patient-rated outcomes								
Health-related quality of life	SF-36 aggregate score*	X	X	X	X	X	X	X
Overall health improvement	CGI-I*				X	X	X	X
Cognitive functioning	CFQ		X	X	X			
Illness perception	b-IPQ		X	X	X	X	X	X
Illness behavior	BRIQ		X	X	X	X	X	X
Symptoms of FSD	BDS Checklist		X		X	X	X	X
Somatic symptoms	SCL-som	X	X	X	X	X	X	X
Symptoms of anxiety and depression	SCL-anx 4 and SCL-depr 6	X	X	X	X	X	X	X
Symptom intensity and interference	NRS		X	X	X	X	X	X
Pain intensity	NRS		X	X	X	X	X	X
Illness worry	Whiteley-6-R	X	X	X	X	X	X	X

Biopsychosocial understanding	PEB-PM		X	X	X	X	X	X
Negative effects of the treatment	INEP				X			
Treatment expectations	CEQ			X				
Expected effect of study drug treatment**	NRS		X					
Patient-clinician alliance	WAI-SR			X	X			
Experience of service	ESQ				X			
Existential needs	SNQ		X					
Experience of meaning in life	SoMe-Da		X		X	X		
Life quality	Danish-EQ-5D-5L		X	X	X		X	X
Clinician-rated outcomes								
Overall health improvement	CGI-I				X			
Diagnosis of multisystem FSD	Diagnostic criteria				X			
Expected effect of study drug	NRS		X					

Register data								
Health-economic data	Danish National Registries (use of healthcare (primary and secondary care visits), prescriptions, sick leave and social benefits)		X					X

5.2. Primary outcome measures

Two primary outcomes measures have been chosen. First, the patient-rated health-related quality of life measured by an aggregate score of the Short-Form Health Survey (SF-36) subscales "physical functioning", "bodily pain", and "vitality" will be used to measure physical health domains usually affected in multisystem FSD [15, 45, 46]. The power calculations presented below are based on this measure. Second, patient-rated overall health improvement will be measured by the 5-point Clinical Global Impression - Improvement Scale (CGI-I). General health is rated as "much worse", "worse", "unchanged", "better", or "much better" in response to the question: "How do you consider your health status now compared with when you first came to the clinic?". This simple and global scale correlates with other specific outcomes in this population, including physical functioning and symptom scores [35, 47, 48] and has been chosen based on recommendations from consensus groups within pain research and functional disorders [49].

5.2. Secondary outcome measures

Illness perception is measured using the Brief-Illness Perception Questionnaire (b-IPQ) [50] and illness behavior is measured using the Behavioral Responses to Illness Questionnaire (BRIQ) [51]. Both illness perception and illness behavior are considered important for the development and persistence of symptoms of multisystem FSD. Health-related physical and psychological functioning will be measured using the relevant subscales of the Symptom Checklist (SCL-92)[52] including somatic symptoms (SCL-som), anxiety and depression (SCL-anx-depr) [53]. The Bodily Distress Syndrome (BDS) checklist [54] will be used to measure the severity of FSD symptoms. Symptom intensity, symptom interference, and pain intensity are measured on a numeric rating scale (NRS) [46]. Cognitive functioning will be measured using the Cognitive Failures Questionnaire (CFQ) [55]. Whiteley-6-R [56, 57] is used to measure illness worry, which is

commonly seen in patients with multisystem FSD and is considered a maintaining factor. This measure has previously been found sensitive to change following PE [25]. The participants' bio-psycho-social understanding of their symptoms will be measured using the questionnaire Patients' Endorsement of a Biopsychosocial Model of Pain/Persistent Somatic Symptoms (PE-BPM) [58]. A nuanced illness understanding has been found to mediate the effect of psychotherapeutic treatment for FSD [24].

The medical doctor rates the overall health improvement using the CGI-I and does a diagnostic reassessment at end of treatment.

5.4. Other measures

5.4.1. Evaluation of treatment

Negative effects of psychological treatment is measured by the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) [59, 60]. Participant's expectations of treatment effects (both PE and study drug treatment) will be measured by the Credibility/Expectancy Questionnaire (CEQ) [61]. For the participants receiving the study drug, the expected effect of the study drug will be measured using a 10-point NRS in response to the question "How effective do you think the study drug will be in improving your overall wellbeing?". Participant's and clinician's relationship will be measured by the Working Alliance Inventory-Short revised (WAI-SR) [62] and their satisfaction with the intervention will be measured with the Experience of Service Questionnaire (ESQ)[63]. Participants will be asked if they have received any other treatment (psychological treatment, physiotherapy, or other) during the trial course.

5.4.2. Existential needs and perspectives

The existential dimension has been proposed to hold independent importance in chronic pain and related conditions [64]. Therefore the existential needs of the participants will be measured using the Spiritual Needs Questionnaire (SNQ) [65], and the subject will be addressed in the qualitative interviews for participants allocated to receive the active PE intervention. Experience of meaning in life is measured using The Sources of Meaning and Meaning in Life, Danish version (SoMe-Da) [66], which is considered important for rehabilitation and reorientation of patients with chronic disease [67].

5.4.3. Economic measures

Data on health economic measures will be collected by using the Danish version of the European Quality of Life–5 dimensions (EQ-D5) [68] and data from Danish National Registries (use of healthcare (primary and secondary care visits), prescriptions, sick leave, and social benefits) [69].

6. Statistics and power calculations

6.1. Power calculations

The power calculations were split into two parts. One concerning the power to detect an effect of PE vs EUC (EDULOX1), and one concerning the effect of duloxetine vs active placebo (EDULOX2). Both power calculations are based on the SF-36 aggregate score and simulations from a constrained linear mixed model (cLMM) with group, time, and their interaction as the only independent variables [70-72]. This model has several parameters: the baseline mean, which is assumed to be the same in all groups; the change from baseline (T0) to before treatment (T1); during treatment (T2); and at end of treatment (T3), respectively; the difference in mean score

between the groups at T1, T2, and T3; and the standard deviations (SD) of the model implied random intercepts and residuals. In all simulations, the probability of making a type-I error was fixed at 0.05.

We first performed simulations of data for the parent trial (EDULOX1), comparing PE (Fig. 1: groups PE, PE+DLX, and PE+PLA) vs EUC (Fig. 1: groups EUC, EUC+DLX, and EUC+PLA). Several scenarios with different values of means and standard deviations were conducted, with the number of participants in the overall study ranging from 350 to 500. Setting the SDs of the random intercepts and residuals at 7 and 4, respectively, and assuming a difference of 2 points on the SF-36 aggregate score at end of treatment (T3) between the two groups (PE vs EUC), gave a power of 96% when n was equal to 400.

Next, we performed simulations of data from the four groups in the nested trial (EDULOX2) (Fig. 1: groups PE+DLX, PE+PLA, EUC+DLX, and EUC+PLA). Using the same SDs as above and assuming a mean difference of 3.5 points between the duloxetine and the active placebo group at end of treatment (T3), the power was calculated to 88% when n is equal to 200.

Experiences from previous studies point towards a low level of dropout (5%)[35]. Hence, a total number of 212 participants in the nested trial and 424 participants in the parent trial were estimated as reasonable sample sizes (PE = 106; PE+DLX = 53; PE+PLA = 53; EUC+DLX = 53; EUC+PLA = 53, and EUC = 106).

The proposed means and SDs were based on data and analyses from previous trial [14-16, 25]. All power calculations were done in Stata 16.1 for Windows, and the Stata scripts used for the calculations are available on request.

6.2. Analysis of outcome measures

Unless we observe serious violations of the underlying model assumptions, the analysis of the SF-36 aggregate score (primary outcome) will be based on the mean difference between groups at

end of treatment (T3), calculated using a cLMM identical to the one described above. In the case of serious violations of model assumptions such as severely skewed residuals and/or random intercepts, variance heterogeneity, etc., we will try to 'tweak' the cLMM to yield correct p-values and CIs with 95% coverage probability by using a non-parametric bootstrap method or by allowing the SDs and correlations to vary between groups.

In the analysis of the CGI-I score (primary outcome) we compare the intervention groups with the control groups using an unadjusted proportional odds model. If the proportional odds assumption is not meet or too few select some of the CGI-I responses, we will combine the responses “much worse”, “worse”, “unchanged”, “better”, and “much better” to give three response groupings (worse, same, or better) and again proceed with an unadjusted proportional odds model.

For the analysis of secondary outcomes, appropriate (generalized) linear mixed models will be used to account for repeated measurements. Depending on the level of measurement of the specific outcome (i.e., categorical, ordinal, binary, or continuous), different distributional families will be specified.

Results will include intention-to-treat analyses and the number needed to treat (NNT). The results will be reported and analyzed in accordance with the Consort Statement. Statisticians are associated with the project.

7. Safety

The safety profile of duloxetine is well-described for patients with fibromyalgia [32]. Safety is assessed by collecting information on adverse events, grade, and attribution at all visits or contacts during the study drug program. Unexpected or serious adverse events will be evaluated by the study sponsor in accordance with Good Clinical Practice (GCP) guidelines.

Participants are instructed to contact the project nurse by phone if experiencing any problems with the study drug, the dose increase, compliance with the trial protocol, or if experiencing intolerable adverse events during the trial and up to 2 weeks after study drug discontinuation. The nurse will have access to advice from medical doctors who will also be available for telephone consultation if requested. Outside office hours, participants should contact their general practitioner or the out-of-hours medical service presenting a card describing the study drug. Project doctors can be contacted by telephone at all times if acute unblinding is required. All phone contacts are registered. A safety plan describing the handling of adverse events and, e.g., study termination has been approved by the GCP unit at Aarhus University.

8. Monitoring and quality assurance

The project will be conducted in accordance with the Helsinki Declaration (II). General procedures for quality control and quality assurance will be followed. All protocol violations will be recorded. The quality and safety of the project are monitored by the GCP unit at Department of Clinical Medicine, Aarhus University.

9. Discussion

This study protocol describes the EDULOX trial, a randomized controlled trial using a nested design consisting of an open-labelled parent trial (EDULOX1) investigating a PE program vs EUC, and a double-blinded nested trial (EDULOX2) investigating duloxetine 60 mg daily vs active placebo. In general, solid and rigidly designed intervention studies for patients suffering from multisystem FSD are highly needed. Internationally as well as nationally, awareness of this patient population is increasing, and easily applicable evidence-based treatment approaches are of great importance.

The EDULOX trial study population is representative of the vast majority of multisystem FSD patients but some restrictions in the inclusion and exclusion criteria have been chosen which are relevant to consider. A relatively young study population has been chosen in order to reduce risk of exclusion based on comorbidity. Furthermore, patients suffering from moderate to severe depression and/or anxiety have been excluded based on the ethical obligation to provide specific treatment for such psychiatric comorbidities and not include in a randomised trial.

Duloxetine is currently widely used in clinical practice, but the evidence base is lacking, necessitating further data on its effect size and side effect profile in this population. Patient education is considered a complementary cornerstone of treatment for FSDs. Patient education may be delivered via different models, for example via groups, technology, or non-medical healthcare professionals, however the context of the intervention is likely to be important[73]. In EDULOX we examine delivery of patient education via extended semi-structured individual consultations with a medical doctor. Clinical experience and current evidence suggests personalization may be key to an effective intervention in this patient group[74]. As this model requires considerable investment of clinician time, further evidence is required for cost-effectiveness analyses.

The EDULOX study design provides a unique opportunity to investigate relevant treatment options both alone and in combination, and opens up the study to a large population of possible participants by offering participation in the parent trial to those not eligible to the nested trial. Performing a large-scale randomized controlled trial in a nested design will provide us with knowledge on how this study design may benefit the scientific investigation of combined interventions suitable for patients with more complex treatment needs.

9.1. Perspectives

The primary goal of this project is to provide evidence for treatments applicable and suitable for the vast majority of patients with multisystem FSD. By focusing on interventions that can be delivered by clinical staff without specialized therapeutic competences, the hope is to support the development of treatment options in less specialized settings, thereby reaching a larger proportion of patients suffering from multisystem FSD. This would prove a valuable foundation when working towards a stepped care model providing better treatment faster for patients who can benefit from less specialized treatment and develop a more sustainable model in which the treatment offered matches the patients' needs. As many clinics currently have waiting lists of more than a year, such accessible treatment options could prove very valuable to patients whose situation both health-related and social may deteriorate significantly while waiting for relevant treatment.

Declaration of Competing Interest

NBF has received consultancy fees from PharmNovo, Vertex, NeuroPN, Saniona, Nanobiotix, and Neurvati, and has undertaken consultancy work for Aarhus University with remunerated work for Biogen, Merz, and Confo Therapeutics. She has received grants from IMI2PainCare an EU IMI 2 (Innovative medicines initiative) public-private consortium and the companies involved are: Grunenthal, Bayer, Eli Lilly, Esteve, and Teva, outside the submitted work.

All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 1

List of serious or unstable somatic illness or conditions that is considered an exclusion criteria

- Stroke
- Alzheimer's disease
- Ischemic heart disease
- Epilepsy
- Fructose intolerance
- Glucosegalactose malabsorption
- Invertase-isomaltase insufficiency
- Increased intraocular pressure
- Uncontrolled narrow-angle glaucoma
- Hemodialysis
- Hemophilia
- Reduced platelet function
- Increased bleeding tendency
- Raynaud's phenomenon
- Uncontrolled hypertension
- Prostate hypertrophy
- Urine retention
- Previous anaphylactic shock

Appendix 2

Adverse events, duloxetine.

*Adverse events, benztropine mesylate

Very common (> 10%)	Nausea*, dry mouth*, headache, somnolence
Common (1-10%)	Decreased appetite, fatigue, weight decrease abdominal pain, diarrhea, dyspepsia, flatulence, constipation, vomiting blood pressure increase, palpitations, muscle spasm, musculoskeletal pain abnormal dreams, anxiety, falls, yawning, lethargy, paresthesia, dizziness, insomnia, tremor, agitation rash*, flushing, increased sweating, abnormal orgasm, dysuria, ejaculation disorder, erectile dysfunction, pollakiuria, decreased libido, blurred vision*, tinnitus
Uncommon (0.1-1%)	Acute liver injury, gastrointestinal hemorrhage, hepatitis, laryngitis, throat tightness, orthostatic hypotension, supra-ventricular arrhythmia (mainly atrial fibrillation), hyperglycemia (reported especially in diabetic patients), increased blood potassium, akathisia, apathy, dyskinesia, gait disturbance, disturbance in attention, disorientation, myoclonus, nervousness*, suicidal ideation, syncope, photo-sensitivity reactions, contact dermatitis, purpura, decreased urine flow, sexual dysfunction, urinary retention, urinary hesitation, visual impairment*, ear pain
Rare (0.01-0.1%)	Haematochezia, hepatic failure, microscopic colitis, stomatitis, eosinophilic pneumonia, hypertensive crisis, interstitial lung disease, dehydration, increased blood cholesterol, hyperprolactinaemia, hyponatremia, hypothyroidism, Schwartz-Bartters syndrome (SIADH), aggression and anger, extrapyramidal symptoms, hallucinations, convulsions, mania, serotonin syndrome, suicidal behavior and ideation, trismus, Stevens-Johnson Syndrome, Allergic reactions, anaphylactic reaction, angio-neurotic edema, glaucoma
Very rare (<0.01%)	Cutaneous vasculitis

Appendix 3

Treatment manual patient education (PE) program

1st individual PE session

Timing: Week 0

Duration: 1.5 hours

Main focus: To develop an individualized case formulation focusing on vulnerabilities, triggers and perpetuating factors based on a bio-psycho-social understanding of multisystem FSD.

Content: Based on information gained from the assessment consultation (family and social background, development of symptoms and disorder, experiences in the health-care system etc.) participant and doctor will address the development of the disorder in the specific life circumstances of the participant. The participants existing illness understanding will be a starting point and the doctor will offer a dialogue aiming to establish a nuanced and helpful illness understanding.

The conversation will be based on a model in which the participant and doctor will discuss vulnerabilities, adaptation strategies, adversities in adult life, triggers for multisystem FSD, reaction to symptoms (emotional and behavioral), current difficulties and resources.

It is encouraged that participant and doctor work on these themes using a whiteboard.

The participant will receive EDULOX homework materials consisting of written PE materials and work sheets to be used in the PE program.

At the end of the session the participant will be offered to take a picture of the information on the whiteboard or copy it in the work sheets (part of the home work materials). The participant will be instructed to orientate themselves in the material and continue to work with the case formulation as preparation for the next individual PE session.

Group PE session

Timing: Week 4

Duration: 3 hours

Main focus: A thorough presentation of the current evidence and clinical experience based knowledge of FSD

Content: Groups of up to 16 patients will be presented with relevant and up to date information in more general terms of the current knowledge and theories regarding FSD thorugh a powerpoint show presented by two members of the clinical staff (at least one medical doctor). The content will include a bio-psycho-social etiology, illness mechanisms, maladaptive illness beliefs and illness behaviors, treatment options and prognosis. The group session will also support the participants engaging in conversation with peers in order to offer the opportunity to recognize themselves in one another and lessen the experience of loneliness or isolation. At the end of the session the participant will choose a focus for making a small change in their everyday life such as diet, sleep or physical movement, and receive educational material matching their choice.

2nd individual PE session

Timing: Week 6

Duration: 1 hour

Main focus: Working with the information the participant has received and reflected upon since 1st individual session and group session. Evaluating the participant's experience with the home work and making a small change in everyday living.

Content: Participant and doctor will have a dialogue based on the participant's experience from the group session and evaluate on the effort made regarding the homework assignment that the participant chose to focus on. Resources and barriers in the process will be addressed aiming to learn from the experience rather than to meet a certain goal. Illness understanding will be further discussed and elaborated on based on the work sheet from the first PE session focusing on any new reflections or perspectives the participant may have thought about regarding their understanding of how they developed multisystem FSD. In the end of the session a new aim or tool (as concrete as possible) is agreed upon as a home assignment prior to the 3rd individual PE session. Possible focus for homework assignment can be stabilizing of diet, sleep, daily activities or physical activity, initiatives towards removing stressors in everyday life, building or confirming resources (relationships, positive thinking, interests etc.) or investigating symptom patterns or triggers. Doctors are encouraged to use a whiteboard for drawing illustrations and to structure the session, and/or use the participant's work sheets from homework materials.

3rd individual PE session

Timing: Week 8

Duration: 1 hour

Main focus: To follow-up on the 2nd PE session and the goal the participant has been working towards and motivate to future self-management.

Content: The 3rd individual PE session assesses the process of working with the agreed goal from the 2nd PE session. The aim is to continue the building of agency and engagement in self-management of the disorder. Again barriers and resources are addressed. Illness understanding is also addressed as a basis for understanding the relevance of the behavior change or use of other tools. Furthermore, the session aims to motivate and engage the participant in future initiatives or

use of behavior focused or other tools to support self-management and agency in regards to their treatment for multisystem FSD in the future.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: